



Contents lists available at ScienceDirect

Physica Medica

journal homepage: <http://www.physicamedica.com>

Original paper

Special radiobiological features of second cancer risk after particle radiotherapy

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ARTICLE INFO

Article history:

Received 30 December 2016
 Received in Revised form 18 April 2017
 Accepted 1 May 2017
 Available online xxx

Keywords:

Second cancer risk
 Particle radiotherapy
 Radiobiology

ABSTRACT

In absolute terms: second cancer risks from radiotherapy of first cancers in adults are small compared to the benefits from radiotherapy but this is not so for radiotherapy of childhood cancers. Moreover, the radiation dose dependence of cancer induction differs between organs and tissues. The organ-specific dose dependence of second cancer risks may indicate the existence of different radiobiological mechanisms. As an inevitable consequence of the age dependence of organ sensitivity to second cancer induction, the organ/tissue weighting factors which have been proposed by ICRP for calculating effective dose (the dose unit Sv) and for risk estimation in the general population should not be used in medical radiation exposures. In adult cancer radiotherapy, the most common unwanted effect is local tumour recurrence whereas both, severe late normal tissue damage and radiation-induced second cancers are rare, around 1% of locally controlled cancer patients. In childhood cancers, local failures are rare (<10% in some cancers) yet second cancers are more common than uncontrolled primaries. The main reason for considering particle radiotherapy for childhood cancers is the possibility to exploit their physical characteristics to reduce the radiation exposure to organs and tissues close to and distant from the primary cancer which is to be targeted. However, the relative biological effectiveness of the radiation doses within the proton beam is not a constant and the relative biological effectiveness of the neutrons is not known as far as the mechanisms of late normal tissue damage and second cancer risk are concerned. In view of the highly charged discussions of the potential risks of treatment-induced second cancers from the neutron contamination of exposure doses in out-of-PTV critical organs a comprehensive European project called ANDANTE was performed which integrated the disciplines of radiation physics, molecular biology, systems biology modelling and epidemiology in order to investigate the RBE of induction of cancer from exposure to neutrons compared to photons. Since out-of-field "effective" neutron doses from proton therapy are smaller than the photon stray doses whichever reasonable RBE is chosen for comparison, and since the absolute risk of radiation-induced second cancer rates are in the order of 1% in the cohorts of adult patients who have been treated in the past with methods which caused relatively high out-of-field doses to large body volumes, it is highly unlikely that such patients treated in future with highly conformal particle therapy are at a higher radiation-induced second cancer risk than those patients treated with photons and described before. Still, the potential risks of second cancers from scattered proton radiotherapy for childhood cancers may cause concern. Yet, the overall risk of undesired consequences of radiation exposure of children which are more complex and manifold than in adult patients (including developmental, neurocognitive, hormonal and growth impairment effects) are likely to be very much reduced by the better focussing of the radiation dose in the target offered by particle radiotherapy. This benefit may far outweigh the still hypothetical second cancer risk from particle radiotherapy in pediatric radiotherapy.

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1. Introduction: The different undesired effects of radiotherapy: their radiobiological mechanisms and impact for treatment planning

This is the art of the Radiation Oncologist: the careful and considerate balance of the potential local tumour control probability

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against the risks of those early, late and very late side effects of radiation exposures to the healthy tissues and organs in and around the cancer tissue which might have serious impact on the quality of life of the individual patient who survived the cancer disease. It is more than 80 years that the German Radiation Oncologist Hermann Holthausen designed a probabilistic model for this balancing act to find, as he called it, the optimal dose in radiotherapy [1]. Ten years after its publication, the Holthausen model was used to

<https://doi.org/10.1016/j.ejmp.2017.05.002>

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analyse radiotherapy results in a real patient cohort, as part of the PhD thesis of Strandqvist who investigated tumour cure and early side effects in a large group of skin cancer patients who were treated with a variety of fractionation and dosage schemes in the Radium Hemmet in Stockholm [2]. From the two sigmoid dose response curves of tumour cure and normal tissue complications which were interpreted by Holthusen as dose dependent probabilities, the dose dependence of uncomplicated cure was calculated. This is now the standard procedure in treatment plan optimisation – yet it should be stressed that two fundamentally different dose dependencies are mathematically processed: whereas the yes/no effect of tumour cure is a typical probabilistic (i.e. stochastic) endpoint, early and late normal tissue effects are not yes/no effects but graded effects, i.e. the severity, not the rate increases with dose.

Moreover, early and late effects show different dependence on time after radiation exposure. The severity of early effects increases with dose after a fixed latency independent of dose. The proportion of patients who exceed an arbitrarily chosen severity threshold of the early side effects is usually taken as response criterion. On the other hand, the severity of late normal tissue effects increases steadily with time after exposure for several years and the damage progression rate increases with dose. Therefore, not the severity but the damage progression rate is the adequate effect criterion, although this is rarely used in clinical research [3].

Finally, for both early and late effects, even more important than dose is the irradiated volume. This is the reason why today treatment plan optimisation is usually based on dose-volume-histograms. The success of modern radiotherapy, however, has produced an unexpected, new side effects of radiation oncology: a clinically significant risk of treatment-induced second cancers. The follow-up studies demonstrate that radiotherapy-associated second cancers are as frequent or more so compared to severe, grade 3/4 late normal tissue damage but have an even longer latency than severe late normal tissue damage. The risk of radiotherapy-associated second cancers appears to depend on radiation dose and radiation dose distribution in the critical organs, and which organs are critical depends on age and sex. The comprehensive review by Berrington-Gonzales [4] suggests that the dose dependence of risk of radiotherapy-induced second cancers in the different organs is, in most organs, compatible with a linear, no threshold dose-effect relationship provided that dose is specified as mean organ dose (with few exceptions such as thyroid and bone marrow). The heterogeneity of factors which influence the second cancer risk in different organs suggests a pronounced heterogeneity of underlying mechanisms. The popular method of pooling and averaging data for the reason of producing statistical significance is likely to produce biological insignificance.

Let us consider first the radiobiology of the four different unwanted effects of definitive radiotherapy in cancer patients and their underlying radiobiological mechanisms as far as they are known:

1. In patients of advanced age (the typical first cancer age) the most common unwanted result of radiotherapy is a local tumour recurrence. This varies between various cancer types from a few % to much more than 50%, depending on affected organ, tumour size and sometimes histopathological factors. Local recurrences are caused by the survival of one or more tumour stem cells in the treated tumour volume, or a geographical miss (which means that not all tumour stem cells were in the planning treatment volume (PTV) and thus were underdosed). The radiobiological mechanism of tumour stem cell inactivation is well known, it is commonly associated with the popular in vitro endpoint of clonogenic inactivation. This itself is related to DNA double strand breaks and unstable chro-

mosome aberrations. This mechanism is specific for tumour cure. Neither in early nor in late normal tissue damage does this cellular radiation mechanism play a significant role [5].

2. The first analysis of radiotherapy patients for finding the optimal dose by Strandqvist used moist desquamation as criterion of severe early complication of radiotherapy. In the early days of radiotherapy this was indeed a major problem in radiation oncology but with the exception of oral mucositis in head and neck cancer patients, early complications are no longer clinically relevant. The pathogenic pathway leads to hypoplasia and inflammation as a multifactorial effect which involves keratinocyte stem cell inactivation, reduced cell production, mitotic cell death and pro-inflammatory responses of the local immune system. There are no good in vitro models for the investigation of this complex response to radiation.
3. The main, if not the only treatment plan optimisation criterion besides tumour control probability, today is late normal tissue damage. The severity of the local pathological effect at particular follow-up times increases with increasing dose. Its impact on pathophysiological signs and symptoms increases with the proportion of the damaged organ parenchyma, not just the volume, but the functional importance of the affected part of the organ for overall organ function. The targets for the pathogenic pathways leading to late radiation damage after radiotherapy are complex. Alterations in structure and function of tissue components such as the microvasculature are key mechanisms to cause radiation injury. Alterations in cell functions are more important than cell proliferation. There is no reliable in vitro model for determining the radiosensitivity for late radiation damage of organs, although some interesting models have been developed and permit the study in vitro of specific pathways to late radiation injury. A good example is the examination of functional radiation effects on microvascular endothelial cells ex vivo. Another example is the study of the radiation-induced activation of fibroblasts in vitro or ex vivo. There is no direct relationship between clonogenic inactivation or related endpoints and the pathogenic pathways leading to late normal tissue damage. Moreover, the disturbance of functional organisation of the tissues in the different organs is the pathological process which leads to atrophy, fibrosis and chronic inflammation. These are the characteristic signs which lead to the symptoms of late normal tissue damage. Therefore, dose-volume-histograms are a poor basis on which to optimise treatment plans in radiation oncology. **Not how much dose but where is the dose is important.** Rather than dose-volume-histograms we need to consider the anatomical distribution of doses.
4. Long after the possible development of late normal tissue damage after radiotherapy we have to expect the development of second cancers. This topic is rather new in radiobiology research, no reliable experimental models are available, most suggestions for pathogenic mechanisms are based on clinical or epidemiological follow-up studies.

2. Radiotherapy-induced second cancers: their dependence on exposed organ, dose, dose distribution, age and gender

The Euratom ALLEGRO project investigated “early and late risks to normal healthy tissues from the use of existing and emerging techniques for radiotherapy” and the relevance of the radiobiological criteria which can be used in radiotherapy treatment plan optimisation. The focus was on radiobiological, pathogenic mechanisms of late normal tissue damage in critical organs, including second cancers and how they are affected by anatomical dose inhomogeneities. Results of a recent Danish study (a cohort and nested case-control study on secondary lung cancer after

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